Lingual Solution Sprays

Lingual Sprays = Solutions containing a drug to be delivered into the oral cavity, either under or over the tongue, by means of a metered dose valve activated by a pump or by a propellant.

Some tests don't apply to lingual sprays containing "true"solutions

Products that are true solutions as opposed to suspensions or micellar "solutions" (more than one phase—one inside the micelle, the micelle wall and a surrounding solution) have different characteristics. A true solution, defined by Webster, is a 'homogenous mixture of a solid, liquid, or gas in a liquid or sometimes a solid or gas". That is, each and every unit of the product has the same composition, so that each given weight of the solution has the same content of drug as every other unit. Because of these differences, the testing requirements for solutions can be reduced. The present draft Guidance in many areas does not make a clean distinction between the testing requirements for solutions and non-solutions. The focus appears to be intended for inhalation or for nasal delivery products.

The following areas typify where lingual solution spray testing might require a different guidance for an NDA CMC section:

Extraction studies

The USP <381> test appears to have been originally developed for parenteral products where the most common solvents were water and low molecular weight solvents. Many lingual sprays use high boiling solvents such a propylene glycol and triglycerides. These high boiling solvents can not be easily concentrated so the extractables can be characterized. The very small amounts extracted from a valve component are lost in the amount of solvent used in the formulation. The use of propellants further restricts the maximum temperature that can be studied for test B to about 40^0 C since most seals begin to fail at about 50^0 C.

Valves

Valves should be treated as other ingredients and components of the product in that once a vendor has been qualified then reduced testing can be carried out. The first three batches of valves would be tested for extractables for the outer seal, the dip tube, the inner seal, and the stem for total weight of extracted material in mg using USP <381> tests A and C. These results would be used to verify the values supplied by the vendor. Thereafter one batch would be tested each year.

Spray Content Uniformity (SCU)

The average amounts of drug and degradants could be determined by spraying 10 activations via a steel canula into suitable solvent. An aliquot of the resulting solution would be assayed for the drug and degradants. Since there is no suction or inhalation on delivering the dose of a lingual solution, this method is more representative of the actual usage and the use of MDI testing equipment is not necessary. Since these valves do not as a rule have residue on the valve surface what leaves the container is what one will find in the solution. In addition, as we are working with a solution as defined above, the amount delivered per activation can most accurately be measured by measuring the weight per activation. The weight of drug would then be the average weight per mg of spray as determined in the average assay times the weight of each activation. This approach conforms in principle with USP <905>, Weight Variation Method, but should be more accurate in that the assumption that the active ingredient is uniformly distributed used for other dosage forms is not needed for the spray as it is a solution and therefore uniform.

SCU Through Container Life

As long as there is no leakage or degradation of the active the concentration of the drug in the solution will remain unchanged so that the same dose will be delivered from first dose to last dose.

Identification of the Drug Substance

The question of the drug identity should be handled the same as for other oral dosage forms ie. assay of the active prior to adding the substance to the batch with the usual assay of the content uniformity and end controls. A special test is not needed as long as the usual manufacturing practices are followed.

Container storage orientations.

We would propose to test the lingual spray solutions in the inverted orientation only. The inverted position is the most stressful as the contact with the valve components is maximized and therefore the product is more likely to fail if there is a problem.

Priming/Repriming in various orientations.

Once primed, the product should not need priming again unless the dip tube is above the solution during activation. The orientation of the dip tube with respect to the solution can be easily seen if the container is a glass bottle. Even with a metal canister it would be most unusual if the patient would hold the container sideways or inverted to spray the solution in to their mouth as the valve caps are molded to fit the index finger only in the upright position. The proper way to hold the container for delivery can be addressed in the labeling or patient instructions by noting that the spray bottle should always be orientated in an upright position so that the dip tube is beneath the level of the solution.

Effect of resting time.

This seems to be only required of inhalation sprays as a solution would not change on resting.

Temperature cycling.

Since the labeling for most lingual spray products would read "store between 15^0 and 30^0C" there would be no need to conduct a cycling program. With MDIs there may some aggregation on freezing that may not reverse on warming. The corresponding event for a solution would be crystallization of the drug substance of one of the excipients that does not dissolve on warming. Such as event can best be observed if it should happen by placing a sample in the refrigerator for a week and seeing if crystals form. If they do then to warm the sample back to room temperature to see if the crystals dissolve.

Effect of orientation.

The performance of the product would be the same as long as the dip tube is under the level of the solution.

Effect of varying flow rates.

As long as a single valve type from a single manufacturer is used for the product there should be no variation in flow rate.

Profiling of Sprays near container exhaustion.

As long as the dip tube is beneath the level of the solution the same weight of spray will be delivered. When the level of solution in the bottle falls to a level such that it can only partially cover the end of the dip tube, a partial dose will be delivered. When the level of the solution can no longer cover the dip tube, no dose will be delivered. There would seem to be no reason to prove this fact for every solution spray.

Due to space constraints not all areas where clarification is needed for lingual solutions are discussed.

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